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Advanced glycation end products and cognitive impairment in schizophrenia

Akiko Kobori[1,2☯], Mitsuhiro Miyashita[1,3,4☯], Yasuhiro Miyano[1,3], Kazuhiro Suzuki[1,4], Kazuya Toriumi[1], Kazuhiro Niizato[3], Kenichi Oshima[3], Atsushi Imai[3], Yukihiro Nagase[4], Akane Yoshikawa[1], Yasue Horiuchi[1], Syudo Yamasaki[5], Atsushi Nishida[5], Satoshi Usami[6], Shunya Takizawa[7], Masanari Itokawa[1,3], Heii Arai[2], Makoto Arai[1]*

1 Department of Psychiatry and Behavioral Sciences, Schizophrenia Research Project, Tokyo Metropolitan Institute of Medical Science, Setagaya-ku, Tokyo, Japan, **2** Department of Psychiatry and Behavioral Science, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan, **3** Department of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital, Setagaya-ku, Tokyo, Japan, **4** Department of Psychiatry, Takatsuki Hospital, Hachioji, Tokyo, Japan, **5** Research Center for Social Science & Medicine, Tokyo Metropolitan Institute of Medical Science, Setagaya-ku, Tokyo, Japan, **6** Graduate School of Education, University of Tokyo, Bunkyo-ku, Tokyo, Japan, **7** Division of Neurology, Department of Internal Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan

☯ These authors contributed equally to this work.
* arai-mk@igakuken.or.jp

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Abstract

Advanced glycation end products play a key role in the pathophysiology of schizophrenia. Cognitive impairment is one of the central features of schizophrenia; however, the association between advanced glycation end products and cognitive impairment remains unknown. This study investigated whether advanced glycation end products affect the cognitive domain in patients with schizophrenia. A total of 58 patients with chronic schizophrenia were included in this cross-sectional study. Plasma advanced glycation end products were measured using high-performance liquid chromatography (HPLC). Neuropsychological and cognitive functions were assessed using the Wechsler Adult Intelligence Scale, Third Version, and the Wisconsin Card Sorting Test Keio-FS version. Multiple regression analysis adjusted for age, sex, body mass index, educational years, daily dose of antipsychotics, and psychotic symptoms revealed that processing speed was significantly associated with plasma pentosidine, a representative advanced glycation end product (standardized β = -0.425; p = 0.009). Processing speed is the cognitive domain affected by advanced glycation end products. Considering preceding evidence that impaired processing speed is related to poor functional outcome, interventions targeted at reducing advanced glycation end products may contribute to promoting recovery of patients with schizophrenia as well as cognitive function improvement.

Introduction

Advanced glycation end products (AGEs), generated via non-enzymatic glycation of reducing sugars with proteins or lipids, have been implicated in various diseases, including

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cardiovascular events in diabetes mellitus [1], chronic renal failure [2], and Alzheimer's disease [3]. Previous cross-sectional studies revealed that plasma pentosidine, a representative AGE, is associated with schizophrenia [4, 5] and is a useful biological marker for the treatment-resistant-like phenotype [6]. Furthermore, a clinical trial using pyridoxamine, which is one of the three forms of vitamin B6 that inhibits AGE formation, showed moderate improvement in psychotic symptoms in patients with schizophrenia with high plasma pentosidine levels [7]. This evidence clearly indicates that AGEs play a key role in the development and pathophysiology of schizophrenia.

Cognitive impairment is one of the main clinical features of schizophrenia. To date, many studies have revealed a significant and stable association between schizophrenia and cognitive impairments, including working memory [8, 9], processing speed [9–11], and executive function [12]. These impairments have been observed even in first-episode psychosis (FEP) [13, 14]. Furthermore, cognitive impairment is related to poor functional outcomes [15–17], such as occupational prognosis, in schizophrenia [15, 18–20]. Importantly, therapeutic interventions targeting cognitive deficits have shown great success not only in the improvement of cognitive function [21, 22] but also in better functional outcomes [23], including occupational conditions [24–27]. In addition, cognitive remediation contributes to the improvement of negative symptoms [28], which is one of the main barriers to achieving recovery [29]. Therefore, it is essential that we understand the importance of cognitive impairment in order to promote the well-being of patients with schizophrenia.

To date, the relationship between AGEs and cognitive function in patients with schizophrenia is unknown. Thus, the aim of the present study was to identify the cognitive domain that is specifically affected by AGEs in order to facilitate functional recovery in patients with schizophrenia.

Materials and methods

Participants

Fifty-eight patients with schizophrenia (mean age: 46.8 ± 11.4 years; 41 men, 17 women), including three patients with schizoaffective disorder, were recruited from Matsuzawa Metropolitan Hospital (Setagaya-ku, Tokyo, Japan) and Takatsuki Hospital (Hachioji, Tokyo, Japan). Patients were diagnosed based on the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. The cohort included 53 inpatients and five outpatients. The demographic and clinical characteristics of the patients are summarized in Table 1. All participants provided written informed consent, and the study protocols were approved by the ethics committees of both participating institutions (Tokyo Metropolitan Matsuzawa Hospital and Tokyo Metropolitan Institute of Medical Science; approval number 17–16). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Measurement of AGEs and other molecules

Fresh plasma and serum samples were collected from all participants. Plasma levels of pentosidine were determined using high-performance liquid chromatography (HPLC) as previously described [30]. In brief, plasma samples were lyophilized and hydrolyzed in 100 μL of 6 N hydrochloric acid for 16 h at 110˚C under nitrogen. Then, the samples were neutralized with 100 μL of 5 N sodium hydroxide and 200 μL of 0.5 M sodium phosphate buffer (pH 7.4), filtered through a 0.5 μm filter, and finally diluted with phosphate-buffered saline. A sample, corresponding to 25 μg of protein, was injected into an HPLC system and fractionated on a C18 reverse-phase column. The effluent was monitored at excitation-emission wavelengths of 335/

Table 1. Participant characteristics.

Variables	*N*	Mean		SD
Age	58	46.8	±	11.4
Sex (male/female, n)	58	41	/	17
Body mass index (kg/m^2)	55	23.1	±	4.1
Hemoglobin A1c (%)	56	5.3	±	0.4
eGFR (ml/min/1.73 m^2)	57	79.9	±	14.6
Pentosidine (ng/ml)	58	72.8	±	50.4
Pyridoxal (ng/ml)	58	6.9	±	3.9
Inpatients/Outpatients (n)	58	53	/	5
Educational years (years)	58	12.4	±	2.9
Onset of disease (years old)	58	24.2	±	9.1
Disease duration (years)	58	22.6	±	12.3
Anti-psychotics (mg/day, CP equivalent)	58	846.3	±	648.2
MS-J (total)	58	4.6	±	4.7
MS-J (positive symptoms)	58	1.8	±	2.5
MS-J (negative symptoms)	58	0.9	±	1.5
MS-J (general symptoms)	58	1.9	±	2.0

Abbreviations. SD, Standard deviation; eGFR, estimated glomerular filtration rate; CP, Chlorpromazine; MS-J, Manchester Scale-Japanese version.

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385 nm using a fluorescence detector (RF-10A; Shimadzu, Kyoto, Japan). Synthetic pentosidine was used as the reference standard to obtain a standard curve. Serum levels of the three forms of vitamin B6 (pyridoxine, pyridoxal, and pyridoxamine) were determined using HPLC at the private clinical laboratory test company SRL (Tokyo, Japan). Other parameters (glycohemoglobin A1C and creatinine) were measured in the blood samples. Glomerular filtration rate was estimated using the Modification of Diet in Renal Diseases study equation.

Assessment of cognitive performance

The Wechsler Adult Intelligence Scale-Third Edition (WAIS-III), composed of verbal intelligence quotient (VIQ), performance IQ (PIQ), and full-scale IQ (FIQ), was used to assess the cognitive function of the patients. The WAIS-III measures four major index scores: (1) verbal comprehension, (2) perceptual organization, (3) working memory, and (4) processing speed.

The Wisconsin Card Sorting Test (WCST) was used to evaluate executive function. In the current study, we adopted the WCST-Keio-FS computer version (WCST-KFS). We selected five outcome measures in the WCST-KFS: (1) categories achieved (CA), (2) total errors (TE), (3) perseverative errors of Milner (PEM), (4) Perseverative errors of Nelson (PEN), and (5) difficulty of maintaining set (DMS).

Assessment of psychotic symptoms

We used the Manchester Scale-Japanese version (MS-J), which was designed to assess the severity of schizophrenia symptoms [31]. It consists of eight sub-clusters, evaluated using a 5-point rating scale. Scores on four scales (depression, anxiety, hallucinations, and coherently expressed delusions) were determined based on patient responses, while scores on the remaining four scales (flattened affect, incongruous affect, psychomotor retardation, incoherence and irrelevance of speech, poverty of speech, and muteness) were determined via observation in the interview. All MS-J assessments were conducted by an experienced clinical psychologist.

Clinical variables

Clinical information such as age, sex, body mass index, duration of illness, age of onset, duration of hospitalization, number of hospitalizations, level of education, and dose of antipsychotic medication were collected from a brief interview at the time of blood collection or from the clinical records of each patient.

Statistical analysis

Demographic data are presented as the mean ± standard deviation (SD). Multiple regression analysis was used to examine whether AGEs were associated with processing speed. The significance level (α) was set to 0.05, for two-tailed tests. All statistical analyses were performed using the Statistical Package for the Social Sciences (version 20.0; IBM Corp., Armonk, NY, USA).

Results

Table 1 shows the characteristics of the participants. Of the 58 patients, 53 (91%) were hospitalized. The mean disease duration and daily dose of antipsychotics were 24.2 (9.1) years (SD) and 846.3 (648.2) mg/day (SD, chlorpromazine equivalent), respectively. Correlation analysis revealed that only processing speed was significantly correlated with plasma pentosidine levels among the subscales of the WAIS-III (S1 Table, Spearman's correlation coefficient = -0.35, $p = 0.006$), while no correlation was found between pentosidine and each item of WSCT (S1 Table). As shown in Table 2, multiple regression analysis adjusted for age, sex [32, 33], body mass index, educational years, daily dose of antipsychotics, and psychotic symptoms demonstrated that processing speed was significantly associated with plasma pentosidine levels (standardized β = -0.425, $p = 0.009$).

Discussion

In this study, we identified that processing speed is the key cognitive domain that is significantly affected by AGEs in patients with schizophrenia. The significance remains even after adjusting for the considerable confounding effects of age, sex, body mass index, educational history, psychological symptoms, and antipsychotic medications. To the best of our

Table 2. Association between pentosidine and processing speed.

	Unadjusted model		Adjusted model 1[a]		Adjusted model 2[b]	
	Standardized β	*p*-value[c]	Standardized β	*p*-value[c]	Standardized β	*p*-value[c]
Pentosidine (ng/ml)	-0.379	0.009	-0.423	0.006	-0.425	0.009
Age (year-old)			0.188	0.465	0.186	0.594
Sex			-0.098	>.99	-0.109	>.99
Body mass index (%)			0.110	>.99	0.091	>.99
Educational years (years)			0.178	0.486	0.173	0.567
Anti-psychotics (mg/day, CP equivalent)					0.020	>.99
Manchester Scale (total score)					-0.048	>.99

Abbreviations: CP; Chlorpromazine.

[a] Adjusted for age, sex, and educational years.

[b] Adjusted for age, sex educational years, daily dose of anti-psychotics, and Manchester scale.

[c] P values adjusted for multiple testing using the Bonferroni method.

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knowledge, this is the first study to specify the cognitive impairment associated with AGEs in patients with schizophrenia.

Our findings are consistent with previous reports indicating that processing speed impairment is related to schizophrenia [9–11] and FEP [13]. Furthermore, two longitudinal studies revealed that processing speed is linked to subsequent functional outcomes [16], including occupational status [20]. This evidence emphasizes that processing speed deficits are a potential intervention target to obtain better functional outcomes in patients with schizophrenia. Indeed, previous studies have demonstrated that cognitive intervention is effective for improving processing speed [22], even for inpatients with schizophrenia [34]. Taken together, these findings have important clinical implications. AGEs may be a valuable biological marker to specifically identify an impaired cognitive domain; therefore, anti-AGE therapy may be a useful treatment option to achieve functional recovery in patients with schizophrenia, especially those with increased AGEs.

The biological mechanism by which AGEs specifically impair processing speed remains to be clarified. First, we must discuss whether peripheral AGEs reflect brain AGEs; Akhter et al. reported that mice fed a high AGE diet showed higher AGE levels in both the serum and brain compared to mice fed a normal AGEs diet [35]. Furthermore, in a human post-mortem study, AGE levels in the cerebrospinal fluid correlated with plasma AGE levels [36]. These reports indicate that an increase in blood AGEs may reflect accumulation of brain AGEs. White matter abnormalities are one possible explanation for the association between AGEs and processing speed. Karbasforoushan et al. reported that processing speed impairment is mediated by white matter integrity [37]. Kochunov et al. showed that white matter disruption, measured by diffusion-weighted imaging, correlated with processing speed in patients with schizophrenia [38]. This relationship was also observed in siblings of patients and was not affected by antipsychotic medications [38]. Similarly, a relationship at the whole-brain level between white matter volume and processing speed was observed in drug-naïve, healthy young people [39]. Son et al. demonstrated a significant negative correlation between plasma pentosidine and white matter integrity in patients with schizophrenia [40]. Furthermore, a study using postmortem brains from patients with multiple sclerosis, white matter disease, showed that binding of AGEs to the receptor for AGEs (RAGE) triggers neuroinflammation and, consequently, leads to white matter damage [36]. The results of these studies suggest that neuroinflammation, which is induced by AGE-RAGE axis interaction, impairs processing speed via white matter disruption in schizophrenia.

Our findings suggest that AGE-reducing therapy may be effective in improving processing speed in patients with schizophrenia. Pyridoxamine, one of the three forms of vitamin B6, inhibits AGE formation by scavenging the AGE precursor. Our previous clinical study demonstrated that pyridoxamine improved psychotic symptoms in some patients with schizophrenia with high plasma pentosidine levels [7]. Furthermore, our data showed that there was a marginally positive association between serum pyridoxal levels and processing speed (S2 Table, Spearman's correlation coefficient = 0.22, $p = 0.093$). These findings indicate the possibility that vitamin B6 administration is an effective approach for improving the processing speed in schizophrenia. Recent investigations have shown a significant association between AGEs and adverse lifestyle habits, including low physical activity [41] and high AGE diets [42]. In fact, aerobic exercise [43] and dietary intervention [44] improved cognitive function in patients with schizophrenia. Further studies are needed to examine the effect of anti-AGE therapies on processing speed and functional outcomes in patients with schizophrenia.

This study has several limitations. First, a cross-sectional design was unable to reveal the direction of the relationship between AGEs and cognitive impairment. A prospective design in future research is needed to address this issue. Second, we should consider the limited

statistical power due to the relatively small sample size. However, the robust significance allows us to interpret that the association between AGEs and processing speed dysfunction is reliable.

Conclusions

In conclusion, we found that the processing speed is specifically related to AGEs. We hope that interventions for AGEs, such as administration of vitamin B6 or modifications of adverse lifestyles, will be useful treatment options to improve patient recovery and cognitive function.

Supporting information

S1 Table. Correlation between pentosidine and cognitive function.
(DOCX)

S2 Table. Correlation between pyridoxal and cognitive performance.
(DOCX)

S1 Raw data.
(XLSX)

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Author Contributions

Conceptualization: Akiko Kobori, Mitsuhiro Miyashita, Yasuhiro Miyano, Makoto Arai.

Data curation: Akiko Kobori, Mitsuhiro Miyashita, Yasuhiro Miyano, Makoto Arai.

Formal analysis: Akiko Kobori, Mitsuhiro Miyashita, Yasuhiro Miyano, Kazuhiro Suzuki, Kazuya Toriumi, Kazuhiro Niizato, Kenichi Oshima, Atsushi Imai, Yukihiro Nagase, Akane Yoshikawa, Yasue Horiuchi, Atsushi Nishida, Satoshi Usami, Makoto Arai.

Funding acquisition: Akiko Kobori, Mitsuhiro Miyashita, Yasuhiro Miyano, Makoto Arai.

Investigation: Akiko Kobori, Mitsuhiro Miyashita, Yasuhiro Miyano, Kazuhiro Suzuki, Kazuya Toriumi, Makoto Arai.

Methodology: Akiko Kobori, Mitsuhiro Miyashita, Yasuhiro Miyano, Makoto Arai.

Project administration: Makoto Arai.

Resources: Mitsuhiro Miyashita, Kazuhiro Niizato, Kenichi Oshima, Atsushi Imai, Yukihiro Nagase.

Supervision: Syudo Yamasaki, Atsushi Nishida, Satoshi Usami, Shunya Takizawa, Masanari Itokawa, Heii Arai, Makoto Arai.

Validation: Mitsuhiro Miyashita, Kazuya Toriumi, Syudo Yamasaki, Shunya Takizawa, Masanari Itokawa, Heii Arai, Makoto Arai.

Writing – original draft: Akiko Kobori, Mitsuhiro Miyashita, Yasuhiro Miyano.

Writing – review & editing: Syudo Yamasaki, Atsushi Nishida, Satoshi Usami, Shunya Takizawa, Masanari Itokawa, Heii Arai, Makoto Arai.

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